REMARKS

Claims 1, 8, 10, 11, and 13 are pending in the application. The various amendments to claim 1 were made merely to conform with formal matters and to further clarify the claimed invention. Further support for the amended claim 1 can be found at least in Fig. 1 of the present application, in which the genes coding for FSH beta and FSH alpha subunits are to be set forth sequentially in the 5' to 3' direction. No new matter has been introduced.

Telephonic Interview

Applicants' representative thanks Examiners Wang and Saoud for courtesies extended during the telephonic interview held on April 22, 2009. No agreement was reached.

Formalities

The Examiner has objected to the drawings/figures under 37 C.F.R. §§1.58(a) and 1.83 allegedly for inappropriate duplication of sequence listings. Applicants respectfully request that this objection be held in abeyance until the application is otherwise in condition for allowance. At which time Applicants will make the necessary revisions to the drawings/figures.

Rejection Under 35 U.S.C. §103

Claims 1, 8, 11, 13 and 17 have been rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 5,674,711 in view of U.S. Application No. 2003144189, U.S. Patent 6,632,637, U.S. Patent 6,136,536, U.S. Application No. 20030083242, U.S. 6,852,510 and further in view of Logan et al. (Proc. Natl. Acad. Sci. USA, 1984, 81:3655-3659) and WO03/048366. Applicants traverse this rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

At the outset, Applicants note that eight (8) references were cited in formulating this rejection. This alone should be an indication of the weakness of the rejection that the Examiner has made. Applicants submit that the citation of eight (8) references to formulate an obviousness rejection is excessive and serves to imply the "non-obviousness" of the rejection.

Lack of prima facie obviousness of the claimed invention - No reasonable expectation of success

US 6,632,637 (the '637 patent) discloses an expression vector that expresses at least two exogenous genes separated by an internal ribosomal entry site (IRES). However, the second coding sequences are those encoding selectable markers such as dihydrofolate reductase. There is no description of the vector construct containing the IRES sequence for the expression of structural gene in the '637 patent. And the '637 patent does not teach or suggest the use of IRES sequence for the expression of structural gene such as human FSH gene. The level of expression of these selectable marker genes was not of any concern in the reference, and as a result, the level of expression of the second gene was not quantitatively studied compared to the first coding sequence. The expression level of the second gene was examined merely as a relative marker value of the first gene expression and used to only gauge the comparative expression activity of the first gene expression. That is, the expression amount of the second gene was not measured relative to the first gene expression. Thus, any quantitative estimation of the second gene expression from the first gene expression is not possible from a reading of the '637 patent. In this regard, the '637 patent fails to disclose or suggest including a second "structural" protein related to the first polypeptide component for which quantitation and relative abundance of expression of the two related genes is desired to be understood. Moreover, the '637 patent fails to disclose or suggest the claimed (FSHbeta)(IRES)(FSHalpha) construct and its use for making a functional human FSH.

US 5,674,711 (the '711 patent) discloses that full biological activity of human FSH requires one to one stoichiometry of the alpha and beta subunits, as the Examiner has already noted (page 9, line 3-4, Final Office Action mailed February 3, 2009). The '711 patent further discloses a recombinant transformant for producing human FSH comprising an expression vector comprising a gene encoding human FSH alpha or beta, a promoter sequence, a polyadenylation (polyA) motif sequence and a dihydrofolate reductase (DHFR) gene.

Given the combination of the above-cited references, a person of ordinary skill in the art would not have been motivated to use the (FSHbeta)(IRES)(FSHalpha) gene construct to make a full FSH protein for which a 1:1 stoichiometry of the subunits is desired with a reasonable expectation of success. While it may have been obvious to try to express the full FSH protein using the (FSHbeta)(IRES)(FSHalpha) construct, it cannot be overlooked that

the '637 patent fails to provide evidence that a one-to-one expression of each of the two subunit polypeptides was produced from the vector. In the absence of such evidence, and in view of the requirement that FSH protein formation be based on the presence of a one to one stoichiometry of it subunits, Applicants assert that the Examiner has failed to meet the burden of establishing *prima facie* obviousness of the claimed invention for the (FSHbeta)(IRES)(FSHalpha) vector construct for expressing human FSH. Accordingly, the presently claimed invention is not obvious over the cited references.

Teaching Away

In addition to the above reasons why the presently claimed invention is not obvious over the cited documents, the Examiner's attention is directed to Mizuguchi et al., "IRES-Dependent Second Gene Expression Is Significantly Lower Than Cap-Dependent First Gene Expression in a Bicistronic Vector", Molecular Therapy, Vol. 1, No. 4, April 2000, pages 376-382 (submitted with the Amendment filed April 3, 2009), which teaches away from the claimed invention. Miguchi discloses that the expression of the IRES-dependent second gene was less efficient than that of the first gene under both *in vitro* and *in vivo* conditions, in most cases between 20 and 50% of the first gene (page 376, Abstract), although more efficient than second gene expression in a plasmid without the IRES (0.1–0.8% of the first gene).

In view of the fact that Miguchi discloses that the level of expression of the second gene product was lower than the expression level of the first gene product, a person of ordinary skill in the art attempting to make human FSH protein would be dissuaded from making the (FSHbeta)(IRES)(FSHalpha) construct to express the FSH protein, because a one to one stoichiometry of the polypeptide subunits expressed from the (FSHbeta)(IRES)(FSHalpha) construct obviously could not be achieved. A person of ordinary skill in the art of making human FSH protein would search for a vector that expresses both FSHbeta and FSHalpha at about the same level so that the full FSH protein can be made efficiently. Thus, the skilled artisan would not have selected the construct of the vector containing IRES sequence for the expression of human FSH gene. In contrast to the Miguchi disclosure, the present application describes a surprising discovery that a full FSH protein can be made efficiently, and that the (FSHbeta)(IRES)(FSHalpha) construct produces one to one stoichiometry of the subunits. Therefore, it is not obvious to one of ordinary skill in the art at the time the instant invention was made to combine the teachings of the cited

references nor would the skilled artisan have been motivated to select the claimed specific construct with any reasonable expectation of success.

In contrast to the disclosure in the cited references and in spite of the deficiencies associated with the disclosures in the cited references, Applicants have unexpectedly successfully produced fully functional human FSH gene product in adequate amounts for further use by using the claimed vectors containing the IRES sequence. Furthermore, the possibility of using IRES sequence for the expression of other proteins such as luteinizing hormone, human chorionic gonadotropin, thyroid stimulating hormone, Factor Ⅷ and IL-12 are also enabled by the present specification, which shows for the first time that IRES can be used to make useful amounts of functional structural proteins.

The vector construct subject matter of Claim 1 is designed to maximize the expression of human FSH that requires the one to one stoichiometry of an alpha and a beta subunit binding

In the vector construct of Claim 1, the expression of the upstream gene from the IRES sequence is mediated by cap-dependent translation and the expression of the downstream gene from the IRES sequence, on the other hand, is mediated by the IRES-dependent translation.

It is conventionally known in the art that the IRES-mediated translation correlates with the length of the core coding sequence (J Virol. 2003 Jul;77(13):7502-9). Thus, the alpha subunit gene with 351 base pairs was positioned downstream of the IRES sequence in the vector construct and the beta subunit gene with 390 base pairs upstream of IRES, by which the problem of low efficiency in second gene expression using IRES sequence was inventively improved. Therefore, the claimed vector construct is inventive and it is not obvious that the skilled artisan would have easily selected the presently claimed construct. Accordingly, the presently claimed invention is patentable over the cited references.

Status of the family of patents related to the present application

For the Examiner's consideration, Applicants provide below the scope of allowed claims in the counterpart foreign applications related to the present application.

(1) The priority Korean patent application was registered in the Korean Intellectual Property Office with the following claims (Korean patent registration Number 10-0533734).

What is claimed is

【claim 1】

An expression vector to express human follicle stimulating hormone (FSH) comprising a gene encoding human FSH, a promoter sequence of early gene of cytomegalovirus (CMV), a tripartite leader sequence of adenovirus, a polyadenylation motif sequence and a dihydrofolate reductase (DHFR) gene.

【claim 2】

The expression vector as set forth in claim 1, wherein the gene encoding human FSH consists of human FSH alpha subunit gene represented by SEQ. ID. No 1, internal ribosomal entry site (IRES) sequence represented by SEQ. ID. No 7 and human FSH beta subunit gene represented by SEQ. ID. No 2.

【claim 3】

The expression vector as set forth in claim 2, wherein the promoter sequence of early gene of CMV is represented by SEQ. ID. No 8.

【claim 4】

The expression vector as set forth in claim 2, wherein tripartite leader sequence of adenovirus is represented by SEQ. ID. No 9.

【claim 5】

The expression vector as set forth in claim 2, wherein the polyadenylation motif is a polyadenylation motif of early gene of SV40 virus, represented by SEQ. ID. No 11, and/or a polyadenylation motif of bovine growth hormone (BGH) gene, represented by SEQ. ID. No 12.

【claim 6】

The expression vector as set forth in claim 2, wherein the dihydrofolate reductase (DHFR) gene is represented by SEQ. ID. No 10.

【claim 7】

A recombinant transformant mass-producing human FSH prepared by introducing the expression vector of claim 1 into host cells.

【claim 8】

The recombinant transformant as set forth in claim 7, wherein the host cell is a Chinese hamster ovary (CHO) originated cell line (CHO/dhfr-) harboring a damaged dihydrofolate reductase (DHFR) gene (Accession No: KCLRF-BP-00082).

【claim 9】

A method for mass-production of human follicle stimulating hormone comprising the following steps of:

1) Preparing an expression vector containing human FSH gene;

2) Transfecting host cells with the expression vector of the step 1);

3) Selecting transformants transfected in the step 2);

4) Selecting a recombinant transformant stably producing human FSH from the recombinant transformants selected in the step 3); and

5) Obtaining human FSH from the culture of the recombinant transformant selected in the step 4).

【claim 10】

The method for mass-production of human follicle stimulating hormone as set forth in claim 9, wherein the expression vector of step 1) is an expression vector of claim 1.

【claim 11】

The method for mass-production of human follicle stimulating hormone as set forth in claim 10, wherein the selected recombinant transformant of step 4) is a transformant of claim 8.

(2) <u>European patent application</u> Examiner stated as follows in its first Office Action:

"The person skilled in the art would have not selected a construct where the IRES is specifically placed between the alpha and the beta subunits of the FSH."

Given the above allowable claims in the Korean Patent Office and the indication of lack of prior art references for the subject matter that is presently sought to be patented in the present application, Applicants assert that the presently claimed invention is free of prior art and is not obvious over the cited references.

<u>Allowable Subject Matter</u>

Applicant acknowledges the Examiner's indication that the subject matter of claim 10 is in allowable condition.

Conclusion

It is believed that the application is now in condition for allowance. Applicants request the Examiner to issue a notice of Allowance in due course. The Examiner is encouraged to contact the undersigned to further the prosecution of the present invention.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to JHK Law's Deposit Account No. **502486** during the pendency of prosecution of this application. Should such additional fees be associated with an extension of time, applicant respectfully requests that this paper be considered a petition therefor.

Respectfully submitted,

JHK Law

Dated: July 3, 2009

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